Remarks

Original claims 18, 19, 22, 23, and 33 are currently pending. Claims 1-17, 21, 24, 26, and 27 were withdrawn. Claims 20, 25, 28, and 29 were cancelled. Claims 30-32 were not entered.

Sequence Listing

Applicants submit herewith a replacement Computer Readable Form (CFR) Sequence Listing. The replacement Sequence Listing is meant to identify the sequence that was previously and unintentionally unidentified in the specification.

Amendment to the Specification

An amendment to the specification is submitted to include sequence identifiers for all sequences that were previously and unintentionally unidentified in the specification.. The amendment contains no new matter.

35 U.S.C. §101 Rejection

The claims stand rejected under 35 U.S.C. §101 for lack of utility. The Examiner states that "Example 7 does not provide evidence that SDF-5 increases cartilage formation in combination with BMP2" (page 3, lines 2-3). Applicants respectfully disagree with the Examiner's conclusions on utility. Applicants respectfully submit that the evidence of cartilage formation is amply demonstrated by the increase in markers for cartilage. These are all extracellular matrix proteins made by cartilage and virtually no other tissue types, and are, therefore, widely regarded as indicative of cartilage and only cartilage. As stated by Pearson and Sasse, JBC, 267(35): 25364-25370 (1992), p. 25364, column 2, "The chondrocyte (cartilage) phenotype is characterized by the coordinate expression of various extracellular matrix proteins including type II, IX, and XI collagens and the large aggregating proteoglycan, aggrecan." Decorin is a small, leucine-rich proteoglycan that is a large component of many extracellular matrices (Id. at p. 25364). The increase of these markers can, therefore, be indicative of the formation of cartilage.

The fact that bone and hypertrophic cartilage markers were significantly decreased or absent in Example 7 (pgs. 52-53 of the specification) does not detract from the fact that markers for cartilage were increased. The decrease or absence of hypertrophic cartilage

markers support the assertion that SDF-5 in combination with BMP-2 is involved in forming only chondrocytes and not osteoblasts because BMP-2 alone increases the expression of hypertropic cartilage and bone marker genes. BMP-2 alone also caused less of an expression of cartilaginous markers than when combined with SDF-5. This is an indication that SDF-5 is involved in the regulation of cartilage formation. It is also significant that SDF-5 in combination with BMP-2 provides a greater enhancement of the cartilage phenotype than PTHrP and BMP-2, as PTHrP is known in the art to direct the formation of chrondrocytes (Kronenberg, H., Nature 423: 332-336 (2003), p. 333). Thus, a greater enhancement suggests that SDF-5 in combination with BMP-2 is involved in the formation of cartilage.

The Official Action indicates that "no one of skill in the art would believe that the invention could be used as suggested" (p. 3, lines 11-12) and that the "suggested uses do not appear to be credible" (p. 3, line 19). Applicants respectfully traverse and include an affidavit by inventor Edward LaVallie asserting that those skilled in the art would indeed accept the results of the experiment described in Example 7 as sufficient data to support the ability of SDF-5 in combination with BMP-2 to form cartilage. Applicants believe that this affidavit is sufficient to establish utility, as the MPEP states at § 2107.03, part VI, "Affidavit evidence from experts in the art indicating that there is a *reasonable* expectation of success, supported by sound reasoning, usually should be sufficient to establish that a utility is *credible*" (Emphasis in original).

Regarding the criteria for credible assertions of utility, Applicants respectfully submit that the Examiner has used too strict a standard. The MPEP states at § 2107.02, part B, that "An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion." Applicants respectfully submit that there are no logical fallacies in the assertion that the increase in cartilage markers indicate an increase in cartilage formation and that this increase can be used to treat cartilage disorders. There is no suggestion that any scientific principle has been violated. The MPEP explicitly supports Applicants' point that it is not necessary to have a successful *in vivo* example to establish a credible utility: "The absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101" (MPEP § 2107.02, part B).

Applicants respectfully believe that the interpretation of the Rosen reference in the Official Action is inaccurate and that the following quoted sentence has been taken out of

context: "We also begin to address the relationship between osteoprogenitor and chondroprogenitor cells as it may relate to endochondral bone formation" is the last sentence at the end of the introduction on p. 1760. Applicants submit that the sentence is meant to be a general characterization of the article. Applicants further submit that the "cells" being referred to are all of the 24 cell lines derived from postcoitus mouse limb bud cells. Not all cell lines expressed chondroblast and osteoblast phenotypes. The "may" in the quoted sentence is therefore referring to all cell lines. Only 4 of the 24 cell lines, for example, synthesized BGP (protein used to determine whether the cell line was chondroblast like) constitutively. Thus, the specific cell line that is included in Example 7, i.e., MLB13MYC 14, was chosen as an example of an early skeletal progenitor cell for the purpose of being characterized. Even if the "may" were directly referring to the MLB13MYC 14 cell line, however, this further does not detract from the asserted utility of the invention because the MPEP makes the point that an application should not be rejected for utility "simply because no animal model for the human disease condition [has] been established," MPEP § 2107.01, part III.

Applicants also refer the Examiner to the preceding paragraph of the Rosen reference at p. 1759, column 2, where it states: "In vitro cells, cells isolated from the developing skeleton are capable of responding to the BMPs, and BMPs can induce these embryonic cells to differentiate into osteoblast-like and chondroblast-like cell types. *These results correlate well with in vivo data on BMP activity*" (Emphasis added). The article also describes how the *in vitro* model has certain advantages over *in vivo* models and was used to obtain data that could not be extrapolated from an *in vivo* experiment (p. 1766, column 2):

> The difficulties inherent in systems in vivo, notably heterogeneity of cell populations, have left doubt about chondroblast to osteoblast transitions. Analysis of clonal cell populations that originate from a single primary chondrocyte have suggested transdifferentiation does occur. Our ability to use clonal cell lines providing homogeneous cell populations offers distinct advantages. By documenting the differentiation of MLB13MYC cells on a molecular and biochemical level, we have provided additional specific evidence for the sequential differentiation of cartilage cells to bone cell phenotypes, data consistent with reports of the ability of osteoprogenitor cells to express chondroblast-like phenotype features in vitro.

Applicants also respectfully submit that the Rosen article was published in the November 11 issue of the *Journal of Bone and Mineral Research* from 1994 rather than the November 9, 2001 date cited by the Examiner. Applicants submit herein a reference for the Examiner's review from September 2001 that characterizes the MLB13MYC clone 14 as

representing "an undifferentiated early skeletal progenitor that differentiates into chondroblasts and then into osteoblasts in response to BMP-2" (Banerjee et al., *Endocrinology* 142(9): 4026-4039 (2001), p. 4033). Accordingly, Applicants respectfully submit that the cell line is an acceptable model and a predictor of chondroblast and osteoblast formation in the presence of BMP-2.

In the Official Action, the Examiner also states that "nothing [in] the cited references suggests or states that the information gained can be directly extrapolated to, or reliably correlated with *in vivo* activity" (p. 5, lines 18-19). Applicants respectfully traverse this assertion as too restrictive. The appropriate criteria is not whether there is a *reliable* correlation, but rather whether there is a *reasonable* correlation. As the Examiner can well appreciate, the difference in these terms is vast. Further, the case law on this point does not require reliability: "A rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). The MPEP summarized this case at § 2107.02, part VII. "Nor must an applicant provide evidence such that it established an asserted utility as a matter of *statistical certainty.*" (Emphasis added). Applicants respectfully submit that they have sufficiently established a reasonable correlation.

In particular, the MLB13MYC cell line is correlated with *in vivo* activity in that successful *in vitro* discoveries are a determinant in performing *in vivo* experiments. As stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985), "*in vitro* results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween." A specific example, furthermore, is stated in Gori *et al.* BIG-3, which was obtained from screening a MLB13MYC clone, was selected for *in vivo* testing based on positive *in vitro* results: "Because BIG-3 was expressed *in vitro* by cells of the osteoblastic lineage, we performed immunohistochemistry to determine whether osteoblasts express BIG-3 *in vivo*" (Gori et al., JBC 276(49): 46515-46522 (2001), p. 46518).

In the Official Action, however, the Examiner states that the Rosen *et al.* reference does not suggest that growth factors potentiating the expression of chondroblast properties are not connected with *in vivo* function (p. 5, lines 21-23). The very next paragraph after the paragraph the Examiner cites, however, is devoted to a discussion on the function of morphogens in the *in vivo* process of expression of a chondroblast-like phenotype.

Although SDF-5 alone does not affect the cartilage cell phenotype, the combination of SDF-5 and BMP-2 caused an increase in cartilage markers as compared to BMP-2 alone.

Thus, SDF-5 in conjunction with BMP-2 perform a regulatory role in the formation of cartilage.

Applicants apologize for not fully describing the "appropriate circumstances" under which it was deemed that *in vitro* data was sufficient to show utility. The quote in the MPEP at § 2107.01 is from the above-cited Federal Circuit case, *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985), where the invention was directed to imidazole derivative compounds, which inhibit the formation of thromboxane, a compound that was believed to be involved in platelet formation. One issue addressed by the court was whether Iizuka's Japanese application constituted sufficient utility to comply with the practical utility requirement of 35 U.S.C. §101 because the invention only had *in vitro* data to support it. The board decided that "Based on the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" (Id. at 1050). The evidence was that *in vitro* tests were performed and compounds were selected for *in vivo* testing based on their pharmacological activity. It was not expected that all compounds that demonstrated pharmacological activity *in vitro* would behave the same *in vivo,* but it is well known in the art that *in vitro* testing "establishes a significant probability that *in vivo* testing for this particular pharmacological activity will be successful" (Id.). The parent compounds had been tested both *in vitro* and *in vivo* but the invention, i.e., the derivatives, were only tested *in vitro*. Based on these facts, the Federal Circuit determined that there was a reasonable correlation between *in vitro* and *in vivo* tests and the data were sufficient to support a utility.

Applicants respectfully point out that the quote attribution in the Official Action is inaccurate. The circumstances surrounding the case that the Examiner cites are less applicable to the current situation than the details of *Cross v. Iizuka,* which involves a specification with only *in vitro* data for the claimed invention. As noted, the Federal Circuit found that this data was sufficient to establish utility. The case cited by the Examiner is less applicable because Applicants are not arguing on the basis of structural similarity to known anticancer agents.

Furthermore, the Examiner cites the MPEP at § 2107.01 under the heading "Substantial Utility" where it states: "A 'substantial utility' defines a 'real world' use." The example set forth therein of an acceptable use is pertinent to the present case: "Both a therapeutic method of treating a known or newly discovered disease and an assay method for

identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use." The claimed innovations of the present invention can be used in the treatment of cartilage disorders (p. 1, lines 9-10 of the specification). Applicants respectfully submit that the situations used in the MPEP as examples requiring further research in no way resemble the current situation. The instant application not only describes the properties of the claimed product, but also asserts the use of the invention for the treatment of cartilage disorders. The disease/conditions are specified in specific examples in the text, such as osteoarthritis, rheumatoid arthritis, and articular cartilage defects (p. 1, lines 10-11 of the specification). Furthermore, the material has the asserted utility in treating cartilage disorders and the product is not an intermediate.

Another suggested utility of the instant invention that has not been previously mentioned is the use of the invention to obtain chondrocytes and cartilage tissue from the *in vitro* experiment to be administered to a patient (see, e.g., p. 2, lines 25-28). The literature indicate that chondrocytes implanted at the site of a chondral defect and treated with chondrocyte-simulating factors may create a tissue closely resembling hyaline cartilage (see, e.g., Gilbert, Amer. J. of Knee Sur., 11(1): 42-46 (1998) p. 45, column 1).

Another suggested utility is to use an embryonic stem cell line (such as the one mentioned in Example 8) and treat it with SDF-5 to cause the formation of cartilage tissue. The resulting cartilage tissue can be inserted into an area of joint damage in a patient. The insertion of cartilage at the site of joint damage can prevent osteoarthritis. This and other such utilities are readily apparent to one of skill in the art.

Applicants respectfully submit that the claims, as amended and presented herewith, are both directed to statutory subject matter and possess the requisite credible real-world utility under §101. Applicants, accordingly, respectfully request that the §101 rejection be reconsidered and withdrawn.

35 U.S.C. 112, first paragraph Rejection

The claims were also rejected under 35 U.S.C. §112, first paragraph for failure to satisfy the utility requirement.

With regard to the Dermer article, Applicants fully comprehend that Dermer does not agree with using *in vitro* experiments as acceptable predictors of *in vivo* behavior. Applicants are merely pointing out that one editorial opinion that is contrary to the commonly-held beliefs in the art is not legitimate proof that Example 7 does not correlate with *in vivo*

activity. Further, the editorial is an opinion and is not relevant to SDF-5 or any protein related to SDF-5. Applicants respectfully submit that the article demonstrates the state of the art at the time the invention was made in that it describes that those skilled in the art find a correlation between *in vitro* and *in vivo* data. The situation described in Dermer is different from the invention, furthermore, in that it has been well established that the *in vitro* cell line correlates well with *in vivo* models.

The Examiner invites Applicants to state that the clone 14 cell line is identical to the source it was derived from. Applicants respectfully point out that it is not necessary for an *in vitro* model to be identical to its source for it to be an acceptable model that is predictive of *in vivo* behavior. The criteria, as established in the aforementioned *Cross v. Iizuka* case, is that *in vitro* results are generally predictive of *in vivo* test results, and that this was considered enough to prove utility *Cross v Iizuka,* 753 F.2d 1040, 1050.

The Official Action finally states that the "Rosen et al reference is not commensurate in scope with the claimed invention" (p. 9, lines 17-18). Applicants respectfully traverse. The reference is meant to describe the model, i.e., the cell line. SDF-5 is being tested in that model. Applicants again refer the Examiner to the Gori article at p. 46518 where he describes that successful *in vitro* testing led to *in vivo* testing. While Kearns does not directly apply the *in vitro* model discussed in the paper to *in vivo* activity, it is reasonable to consider a correlation between the article and *in vivo* models because successful *in vitro* models are considered a determinant for successful *in vivo* experiments.

Applicants respectfully submit that the §112, first paragraph, rejection has been overcome, and Applicants request that the §112 rejection be reconsidered and withdrawn.

In view of the above amendments and remarks, Applicants respectfully submit that the outstanding §101 and §112 rejections have been overcome and the case is in condition for allowance. Applicants, accordingly, respectfully request that a timely Notice of Allowance be issued in this case.

Should the Examiner have any further suggestions or observations that would facilitate further prosecution or allowance of this case, the Examiner is invited to contact Applicants' representative, designated below.

Respectfully submitted,

Date: May 12, 2004

Raymond Van Dyke
Reg. No. 34,746

Nixon Peabody LLP
Suite 900
401 9th Street
Washington D.C. 2004-2128
Tel: (202) 585-8250
Fax: (202) 585-8080